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Acute Myeloid Leukemia Evolving From Essential Thrombocythemia in Two Patients Treated With Hydroxyurea

James L. Furgerson, Svetislava J. Vukelja, W. Jeffrey Baker, and Timothy J. O'Rourke
Department of Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas

Essential thrombocythemia (ET) is an uncommon myeloproliferative disorder, which is thought to develop from a multipotent stem cell. Like other myeloproliferative diseases, ET is associated with an increased risk of development of acute leukemia (AL). However, the large majority of cases of leukemic transformation in ET are thought to be related to prior therapy, usually radioactive phosphorous or alkylating chemotherapy, and the development of AL in ET is extremely rare in the untreated patient. In this report, two cases of ET which evolved into AL without prior exposure to radiation or alkylating agents, and which were treated with long-term hydroxyurea therapy, are described. The first case had cytogenetic changes in the bone marrow suggestive of therapy-associated leukemia, and the second developed myelodysplastic syndrome on therapy which was likely chemotherapy-induced and led to acute leukemia. Prolonged used of hydroxyurea in patients with ET may lead to therapy-associated acute leukemia. © 1996 Wiley-Liss, Inc.*

Key words: acute myeloid leukemia, essential thrombocythemia, hydroxyurea, thrombocytosis, therapy-associated leukemia, chromosomal aberrations

INTRODUCTION

Essential thrombocythemia (ET) is a myeloproliferative disorder, first described in 1934 by Epstein and Goedel [1], which represents a clonal disorder of a multipotent stem cell. As defined by the Polycythemia Vera Study Group (PVSG) [2,3], ET is characterized by a platelet count $>6 \times 10^5/mm^3$, absence of the Philadelphia chromosome, hemoglobin <13 g/dl, adequate iron stores, absence of myelofibrosis, and no evidence of any other cause of thrombocytosis.

Myeloproliferative disorders are associated with an increased risk of developing acute leukemia. Chronic myelogenous leukemia (CML) has the highest rate of acute leukemic transformation and is followed by polycythemia vera (PV) [4]. The risk is significantly increased in patients treated with alkylating agents or radioactive phosphorous (^{32}P) [5]. In contrast, spontaneous leukemic transformation has rarely been reported in ET [6]. Indeed, in virtually all of the reported cases the process of leukemic transformation has been associated with the use of alkylating agents or ^{32}P. This has led to the abandonment of these agents as first-line therapy in ET, in favor of hydroxyurea. It is thought that hydroxyurea is less leukemogenic, although there is limited data available to substantiate this claim [7]. This report describes 2 patients with ET who were treated with hydroxyurea alone without prior exposure to alkylating agents or ^{32}P, and who developed acute myelogenous leukemia (AML) after several years of daily therapy with hydroxyurea.

CASE REPORTS

Case 1

A 62-year-old man with symptomatic benign prostatic hypertrophy was noted to have thrombocytosis on preoperative evaluation for transurethral resection of the prostate. The patient had a history of peripheral vascular

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Address reprint requests to Cpt. James L. Furgerson, M.D., Department of Medicine, Brooke Army Medical Center, Fort Sam Houston, TX 78234-6200.

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disease manifested by amaurosis fugax, and had documented bilateral carotid stenosis. He was on daily aspirin, which was controlling his neurologic symptoms at the time of initial evaluation. Physical examination at presentation revealed no hepatosplenomegaly and was otherwise unremarkable. Complete blood count revealed a platelet count of $1.0 \times 10^6/mm^3$, hemoglobin of 13 g/dl, and white blood count (WBC) of $6.6 \times 10^3/mm^3$. The initial laboratory evaluation included a normal leucocyte alkaline phosphatase (LAP) score, serum B12, and folate. The peripheral smear revealed thrombocytosis but was otherwise unremarkable. A bone marrow biopsy and aspirate revealed a hypercellular marrow with adequate iron stores, increased numbers of megakaryocytes, and giant platelets. Cytogenetic analysis was normal. The diagnosis of ET was made. Two months later the patient developed tinnitus and lightheadedness, and was started on 1,500 mg of hydroxyurea daily. Within 4 weeks of therapy the platelet count fell to $2.66 \times 10^5/mm^3$ and led to resolution of his symptoms. The patient remained asymptomatic on hydroxyurea, with doses between 1,000–1,500 mg/day, for $10\frac{1}{2}$ years, when he presented with respiratory distress, hemoptysis, and fever. Chest roentgenogram revealed diffuse alveolar infiltrates, and the patient developed respiratory failure shortly after admission. Laboratory data on admission revealed hemoglobin of 12 g/dl, platelet count of $1.50 \times 10^5/mm^3$, and white blood count of $3.78 \times 10^4/mm^3$. Upon review of the peripheral smear, there were 28% circulating blasts. Auer rods were not seen. Bone marrow revealed 35% blasts, with decreased megakaryocytes. Special stains were positive for Sudan black, and negative for nonspecific esterase and periodic acid Schiff (PAS), consistent with AML French-American-British (FAB) type M2. Cytogenetic analysis revealed del(5)(q23), del(7)(q31), inv(16)(p13q22),+8. The patient was begun on high-dose cytosine arabinoside; however, he developed septic shock, multiorgan system failure, and refractory hypotension, and he died on the fifth hospital day. Postmortem examination revealed acute leukemia with leukemic infiltrates in the liver, kidneys, lungs, myocardium, and epicardial arteries.

Case 2

A 59-year-old man with hypertension and a history of transient ischemic attacks (TIA)s, on daily aspirin and dipyridamole, was admitted for an acute upper gastrointestinal (GI) bleed. The patient was transfused 4 units of packed red cells. Aspirin and dipyridamole were discontinued. An elevated platelet count of $1.4 \times 10^6/mm^3$ was noted. Approximately 4 weeks later, the patient complained of diplopia, lightheadedness, and occasional transient left arm paresthesias. Due to the patient's symptoms and elevated platelet count, he was referred to hematology for further evaluation. Physical examination was significant for splenomegaly. Laboratory data revealed a hemoglobin of 15 g/dl, WBC of $1.4 \times 10^4/mm^3$, and platelet count of $1.09 \times 10^6/mm^3$. The peripheral smear revealed thrombocytosis but was otherwise unremarkable. LAP score was 199. No red cell mass was performed. A bone marrow exam revealed a hypercellular marrow with a myeloid:erythroid (M:E) ratio of 4:1. Iron stores were normal. Megakaryocytes were present in markedly increased numbers. Cytogenetic studies were normal. The diagnosis of ET was made, and aspirin and dipyridamole therapy was reinstituted with some improvement. However, within 1 month the patient suffered a cerebrovascular accident with profound left hemiparesis, and hydroxyurea was initiated. The patient received between 500–3,000 mg/day of hydroxyurea, with excellent control of platelets of $2.00–4.00 \times 10^5/mm^3$, and resolution of all neurologic symptoms. After 7 years of therapy with hydroxyurea the patient developed pancytopenia. The dose of hydroxyurea was decreased with no significant improvement in the cell counts. Peripheral blood film showed macrocytic anemia and few circulating blasts. The hydroxyurea was stopped and a bone marrow exam was performed, revealing trilineage hyperplasia with marked dyspoiesis, and an increase in ringed sideroblasts consistent with myelodysplastic syndrome. Cytogenetic analysis at that time was normal. The patient developed progressive splenomegaly and worsening cytopenias. Three months later a repeat bone marrow exam revealed acute myelogenous leukemia, FAB subtype M4. No cytogenetic analysis was performed. He was induced with mitomycin and hydroxyurea and failed to achieve response, and then was treated with cytosine arabinoside. The patient's treatment was complicated by neutropenia, which was followed by sepsis and multiorgan system failure. Death ensued within 8 weeks of the diagnosis of AML.

DISCUSSION

Therapy-associated acute leukemias (T-AL) have been increasingly recognized in recent years and now account for >20% of all acute leukemias [8,9]. The highest risk of T-AL has been associated with combined therapy using alkylating agents and radiation in the treatment of lymphomas [10,11]. It has also been noted following prior diagnosis of myeloproliferative disorders. The incidence of AL in polycythemia vera is thought to increase from 1–2% in those treated with phlebotomy alone to 10–15% in those treated with alkylating agents or ^{32}P [4,5]. Of 51 patients with PV enrolled in PVSG protocol 08, where hydroxyurea was employed as the only myelosuppressive treatment, four cases of AL developed after 8 years. When compared with a historical control group of those treated with phlebotomy alone, the incidence of AL was significantly higher in the hydroxyurea-treated group [12–14]. The use of alkylating agents and ^{32}P in ET has also been

associated with T-AL. In an exhaustive review of the literature in 1986, Sedlacek et al. [15] reported 15 cases of acute leukemia in ET patients. Only one case had no history of exposure to ^{32}P or an alkylating agent, and received no myelosuppressive treatment [16]. Thus, evolution of ET to acute leukemia is extremely rare in the untreated patient, and usually appears in the setting of previous chemotherapy [17]. T-AL is characterized by more frequent cytogenetic abnormalities and a very poor prognosis, with complete remission (CR) rates <20% and long-term disease-free survival (DFS) <5% [9]. The most commonly observed cytogenetic abnormalities associated with T-AL involve chromosomes 5 and 7 [18–20]. In this report, two cases of ET with leukemic transformation are presented without prior exposure to agents historically associated with T-AL. However, daily use of hydroxyurea for periods of 7 and 10 years may have led to development of T-AL. It is interesting that one case showed cytogenetic changes well-described in T-AL, and the other demonstrated a likely therapy-induced myelodysplastic syndrome prior to the development of frank acute leukemia. Regrettably, no initial red cell mass was performed in case 2, and the possibility of PV cannot be excluded with certainty. We feel this is an unlikely scenario, however, as the patient had a normal hemoglobin concentration. Nevertheless, such "borderline" cases have been reported to have the same evolution as ET [6].

The carcinogenic potential of hydroxyurea has been considered "uncertain" [7]. Several reports of possible T-AL with hydroxyurea were found upon a review of the literature [6,21–24]. Hydroxyurea is an inhibitor of ribonucleotide reductase, which catalyzes the conversion of ribonucleotide diphosphates to deoxyribonucleotide diphosphates, which can in turn be used for DNA synthesis and repair. Thus, hydroxyurea enhances the effects of ionizing radiation by inhibiting the repair of radiation-induced DNA damage. This specific activity allows the selective killing of cells in the S-phase of cellular reproduction. Cytotoxicity is directly related to dose and duration of exposure [7]. The use of hydroxyurea induces megaloblastic changes in marrow precursor cells, which implies abnormal progression of nuclear maturation and division, which reflects some degree of DNA aberration.

Although hydroxyurea has been evaluated in a number of malignant diseases, it is not considered standard therapy for any solid tumor, and one of its principal uses has been in the myeloproliferative diseases, including ET, where it has been used increasingly to replace more toxic agents over the last 10–12 years. Given this timetable, it is not surprising that cases of leukemic transformation in ET may now be appearing. Such a time course is not typical of cases of T-AL which develop after use of alkylating agents. It seems likely that the very low incidence of leukemic transformation in ET may be significantly enhanced by the use of hydroxyurea. Although a recent prospective, randomized trial demonstrated the efficacy of hydroxyurea in both decreasing platelet count and preventing thrombotic complications after a median of 27 months of follow-up [25], such a trial of sufficient length to assess for T-AL in ET is currently lacking.

As ET is an indolent disorder with a normal life expectancy [26], the use of hydroxyurea should continue to be used cautiously only in symptomatic patients with ET when other agents have failed. Extreme caution should be used in younger patients with ET. These patients usually have milder disease, and tolerate the symptoms better; early exposure to hydroxyurea should be avoided if possible [27]. Alternate treatments for ET should continue to be sought and assessed [28]. The use of hyroxyurea in a large number of patients with sickle cell anemia may shed additional light on the potential leukemogenic effects of hydroxyurea [29,30].

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